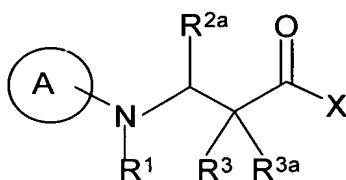


**WHAT IS CLAIMED IS:**

1. A compound of Formula (I):



10

wherein:

15  $R^1$  is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

20  $R^3$  and  $R^{3a}$  are independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, haloalkoxy, alkylthio, or  $-(Alk^b)_m R^b$  in which  $Alk^b$  is a  $C_{1-3}$ alkylene chain,  $m$  is 0 or 1 and  $R^b$  is hydroxy, thiol, nitro, cyano, carboxy,  $-CO_2R^c$  (wherein  $R^c$  is alkyl),  $-SO_3H$ ,  $-SOR^c$ ,  $-SO_2R^c$ ,  $-SO_3R^c$ ,  $-OCO_2R^c$ ,  $-C(O)H$ ,  $-COR^c$ ,  $-OCOR^c$ ,  $-CSR^c$ ,  $-NR^dR^e$  (wherein  $R^d$  and  $R^e$  are independently hydrogen, alkyl, or substituted alkyl),  $-CONR^dR^e$ ,  $-OCONR^dR^e$ ,  $-NR^dCOR^e$ ,  $-CSNRR^dR^e$ ,  $-NR^dCSR^e$ ,  $-SO_2NR^dR^e$ ,  $-NR^dSO_2R^e$ ,  $-NR^dCONR^eR^f$  (where  $R^f$  is hydrogen alkyl, or substituted alkyl) or  $-Nr^dSO_2NR^eR^f$ ;

25  $X$  is selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyoxy, substituted heterocyclyoxy and  $-NR''R''$  where each  $R''$  is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted

alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

A is an aryl, heteroaryl, cycloalkyl, or heterocyclic group wherein said aryl, heteroaryl, cycloalkyl, or heterocyclic group is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclxy, substituted heterocyclxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where each R is independently hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl, -NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic, -NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl, -NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted heterocyclic where R is hydrogen or alkyl, -N[S(O)<sub>2</sub>-R']<sub>2</sub> and -N[S(O)<sub>2</sub>-NR']<sub>2</sub> where each R' is independently selected from the group consisting of alkyl, substituted alkyl,

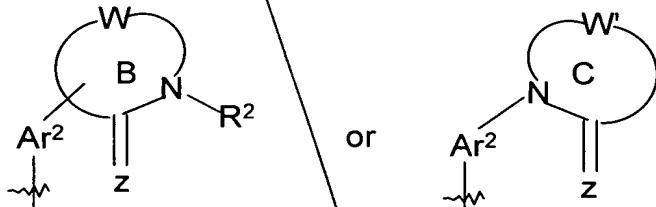
aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

$R^{2a}$  is either:

(i) an  $-Ar^1-R^9$  group where  $Ar^1$  is aryl or heteroaryl optionally substituted with one or two substituents selected from the group consisting of hydroxy, acyl, acylamino, aminoacyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, aminoacyl, aminocarbonyloxy, carboxyl, carboxylalkyl, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, halo, nitro provided that said acyl, acylamino, acyloxy, substituted alkyl, substituted alkoxy and substituted thioalkyl do not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group; and  $R^9$  is selected from the group consisting of acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, oxycarbonylamino, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino, aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl provided that when  $R^9$  is acylamino or acyloxy then the acylamino or acyloxy group does not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group; or

(ii) a group of formula (a) or (b):

20



25

wherein:

$Ar^2$  is an aryl or heteroaryl group optionally substituted, in addition to ring B or C, with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino,

substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl,  
5 substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxyl, substituted alkylsulfoxyl, alkylsulfonyl, and substituted alkylsulfonyl;

10 Z is -O- or -S-;

B is a group wherein W, together with  $-C(=Z)NR^2-$ , forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and  $-SO_n-$  (where n is 0 to 2) wherein said saturated or unsaturated  
15 heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group  
20 consisting of with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy,  
25 (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio,  
30 substituted alkylthio, alkylsulfoxyl, substituted alkylsulfoxyl, alkylsulfonyl,

1000 999 998 997 996 995 994 993 992 991 990 989 988 987 986 985 984 983 982 981 980 979 978 977 976 975 974 973 972 971 970 969 968 967 966 965 964 963 962 961 960 959 958 957 956 955 954 953 952 951 950 949 948 947 946 945 944 943 942 941 940 939 938 937 936 935 934 933 932 931 930 929 928 927 926 925 924 923 922 921 920 919 918 917 916 915 914 913 912 911 910 909 908 907 906 905 904 903 902 901 900 899 898 897 896 895 894 893 892 891 890 889 888 887 886 885 884 883 882 881 880 879 878 877 876 875 874 873 872 871 870 869 868 867 866 865 864 863 862 861 860 859 858 857 856 855 854 853 852 851 850 849 848 847 846 845 844 843 842 841 840 839 838 837 836 835 834 833 832 831 830 829 828 827 826 825 824 823 822 821 820 819 818 817 816 815 814 813 812 811 810 809 808 807 806 805 804 803 802 801 800 799 798 797 796 795 794 793 792 791 790 789 788 787 786 785 784 783 782 781 780 779 778 777 776 775 774 773 772 771 770 769 768 767 766 765 764 763 762 761 760 759 758 757 756 755 754 753 752 751 750 749 748 747 746 745 744 743 742 741 740 739 738 737 736 735 734 733 732 731 730 729 728 727 726 725 724 723 722 721 720 719 718 717 716 715 714 713 712 711 710 709 708 707 706 705 704 703 702 701 700 699 698 697 696 695 694 693 692 691 690 690 689 688 687 686 685 684 683 682 681 680 680 679 678 677 676 675 674 673 672 671 670 670 669 668 667 666 665 664 663 662 661 660 660 659 658 657 656 655 654 653 652 651 650 650 649 648 647 646 645 644 643 642 641 640 640 639 638 637 636 635 634 633 632 631 630 630 629 628 627 626 625 624 623 622 621 620 620 619 618 617 616 615 614 613 612 611 610 610 609 608 607 606 605 604 603 602 601 600 600 599 598 597 596 595 594 593 592 591 590 590 589 588 587 586 585 584 583 582 581 580 580 579 578 577 576 575 574 573 572 571 570 570 569 568 567 566 565 564 563 562 561 560 560 559 558 557 556 555 554 553 552 551 550 550 549 548 547 546 545 544 543 542 541 540 540 539 538 537 536 535 534 533 532 531 530 530 529 528 527 526 525 524 523 522 521 520 520 519 518 517 516 515 514 513 512 511 510 510 509 508 507 506 505 504 503 502 501 500 500 499 498 497 496 495 494 493 492 491 490 490 489 488 487 486 485 484 483 482 481 480 480 479 478 477 476 475 474 473 472 471 470 470 469 468 467 466 465 464 463 462 461 460 460 459 458 457 456 455 454 453 452 451 450 450 449 448 447 446 445 444 443 442 441 440 440 439 438 437 436 435 434 433 432 431 430 430 429 428 427 426 425 424 423 422 421 420 420 419 418 417 416 415 414 413 412 411 410 410 409 408 407 406 405 404 403 402 401 400 400 399 398 397 396 395 394 393 392 391 390 390 389 388 387 386 385 384 383 382 381 380 380 379 378 377 376 375 374 373 372 371 370 370 369 368 367 366 365 364 363 362 361 360 360 359 358 357 356 355 354 353 352 351 350 350 349 348 347 346 345 344 343 342 341 340 340 339 338 337 336 335 334 333 332 331 330 330 329 328 327 326 325 324 323 322 321 320 320 319 318 317 316 315 314 313 312 311 310 310 309 308 307 306 305 304 303 302 301 300 300 299 298 297 296 295 294 293 292 291 290 290 289 288 287 286 285 284 283 282 281 280 280 279 278 277 276 275 274 273 272 271 270 270 269 268 267 266 265 264 263 262 261 260 260 259 258 257 256 255 254 253 252 251 250 250 249 248 247 246 245 244 243 242 241 240 240 239 238 237 236 235 234 233 232 231 230 230 229 228 227 226 225 224 223 222 221 220 220 219 218 217 216 215 214 213 212 211 210 210 209 208 207 206 205 204 203 202 201 200 200 199 198 197 196 195 194 193 192 191 190 190 189 188 187 186 185 184 183 182 181 180 180 179 178 177 176 175 174 173 172 171 170 170 169 168 167 166 165 164 163 162 161 160 160 159 158 157 156 155 154 153 152 151 150 150 149 148 147 146 145 144 143 142 141 140 140 139 138 137 136 135 134 133 132 131 130 130 129 128 127 126 125 124 123 122 121 120 120 119 118 117 116 115 114 113 112 111 110 110 109 108 107 106 105 104 103 102 101 100 100 99 98 97 96 95 94 93 92 91 90 90 89 88 87 86 85 84 83 82 81 80 80 79 78 77 76 75 74 73 72 71 70 70 69 68 67 66 65 64 63 62 61 60 60 59 58 57 56 55 54 53 52 51 50 50 49 48 47 46 45 44 43 42 41 40 40 39 38 37 36 35 34 33 32 31 30 30 29 28 27 26 25 24 23 22 21 20 20 19 18 17 16 15 14 13 12 11 10 10 9 8 7 6 5 4 3 2 1 0

substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

5       $R^2$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

10      $C$  is a group wherein  $W'$ , together with  $-C(=Z)N-$ , forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and  $-SO_n-$  (where  $n$  is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, alkylenedioxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino,  $N$ -acyl- $N$ -alkylamino, substituted  $N$ -acyl- $N$ -alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino,  $N$ -(alkylsulfonyl)- $N$ -alkylamino, substituted  $N$ -(alkylsulfonyl)- $N$ -alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, nitro, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxyl, substituted alkylsulfoxyl, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

15     (iii) HetAr where HetAr is a nitrogen containing heteroaryl that is optionally substituted with an aryl or substituted aryl group;

20     and enantiomers, diasteromers and pharmaceutically acceptable salts

25     thereof;

and further wherein the compound of Formula I has a binding affinity to VLA-4 as expressed by an  $IC_{50}$  of about  $15\mu M$  or less.

2. The compound of Claim 1 wherein  $R^{2a}$  is an  $-Ar^1-R^9$  group wherein  $Ar^1$  and  $R^9$  are as defined above.

5

3. The compound of Claim 1 wherein  $Ar^1$  is phenyl with the  $R^9$  in the *para* position of the phenyl ring.

10

4. The compound of Claim 3 wherein  $R^9$  is selected from the group consisting of  $-O-Z^a-NR^{11}R^{11'}$  and  $-O-Z^a-R^{12}$  wherein  $R^{11}$  and  $R^{11'}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, and where  $R^{11}$  and  $R^{11'}$  are joined to form a heterocycle or a substituted heterocycle,  $R^{12}$  is selected from the group consisting of heterocycle and substituted heterocycle, and  $Z^a$  is selected from the group consisting of  $-C(O)-$  and  $-SO_2-$ .

15

5. The compound of Claim 4 wherein  $R^9$  is  $-OC(O)NR^{11}R^{11'}$ .

20

6. The compound of Claim 1 wherein  $Ar^1$  is phenyl with a  $-OCON(CH_3)_2$  group at the *para* position of the phenyl ring.

25

7. The compound of Claim 1 wherein A in the above compounds is heteroaryl optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

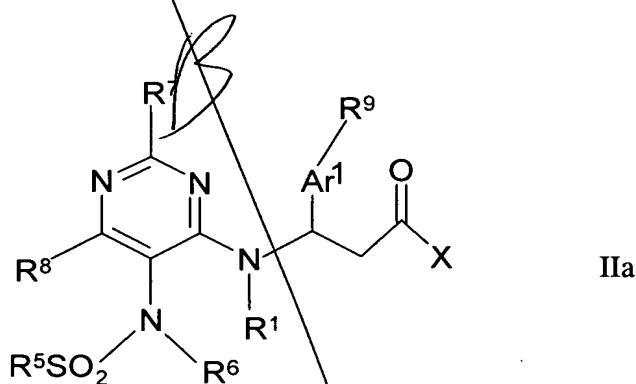
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8. The compound of Claim 1 wherein A is selected from the group consisting of 1-oxo-1,2,5-thiadiazole, 1,1-dioxo-1,2,5-thiadiazole, pyridazine, pyrimidine or pyrazine wherein said rings are optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

5

10. The compound of Claims 1-8 wherein R<sup>1</sup>, R<sup>3</sup> and R<sup>3a</sup> are hydrogen, and X is hydroxyl.

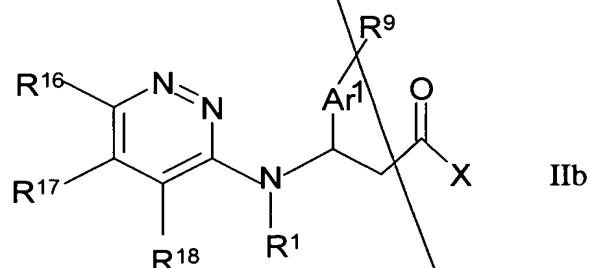
15. The compound of Claim 1 wherein the compound has formula IIa, IIb, IIc, IId or IIe:



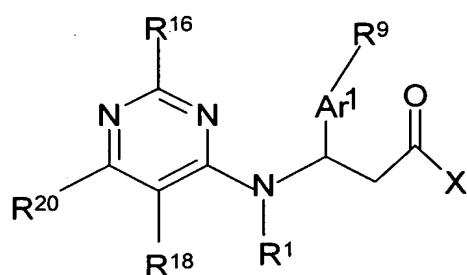
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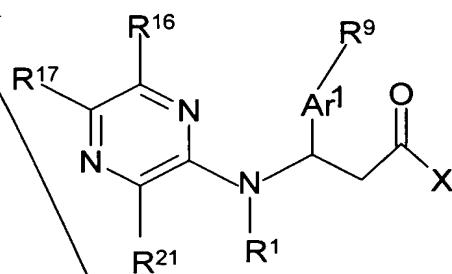


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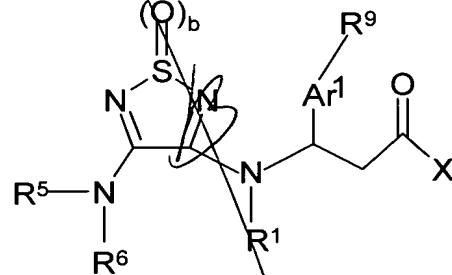
IIc

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IIId

15



IIe

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wherein X is hydroxy or alkoxy;

R<sup>1</sup> is hydrogen;

R<sup>5</sup> is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -SO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is selected from the

group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of

5 hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of

10 hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

15 R<sup>18</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R<sup>20</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

20 R<sup>21</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

b is 1 or 2;

25 Ar<sup>1</sup> is aryl or heteroaryl optionally substituted with one or two substituents selected from the group consisting of hydroxy, acyl, acylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, aminoacyl, aminocarbonyloxy, carboxyl, carboxylalkyl, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, halo, nitro provided that said

30 acyl, acylamino, acyloxy, substituted alkyl, substituted alkoxy and substituted

thioalkyl do not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group; and

*R<sup>9</sup>* is selected from the group consisting of acyl, acylamino, acyloxy, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, oxycarbonylamino, oxythiocarbonylamino, thioamidino, thiocarbonylamino, aminosulfonylamino, aminosulfonyloxy, aminosulfonyl, oxysulfonylamino and oxysulfonyl provided that when *R<sup>9</sup>* is acylamino or acyloxy then the acylamino or acyloxy group does not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group;

10 and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.

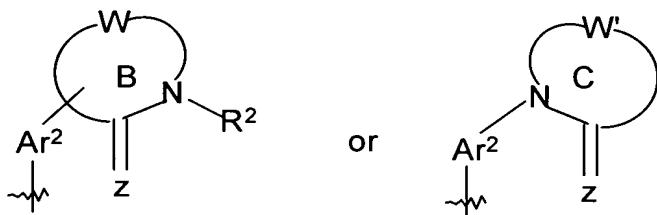
11. The compound of Claim 10 wherein Ar<sup>1</sup> is phenyl, pyridinyl, or pyrimidinyl ring.

15 12. The compound of Claim 11 wherein R<sup>9</sup> is selected from the group consisting of -O-Z<sup>a</sup>-NR<sup>11</sup>R<sup>11'</sup> and -O-Z<sup>a</sup>-R<sup>12</sup> wherein R<sup>11</sup> and R<sup>11'</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, and where R<sup>11</sup> and R<sup>11'</sup> are joined to form a heterocycle or a substituted heterocycle, R<sup>12</sup> is selected from the group consisting of heterocycle and substituted heterocycle, and Z<sup>a</sup> is selected from the group consisting of -C(O)- and -SO<sub>2</sub>-.

20 25 13. The compound of Claim 12 wherein R<sup>9</sup> is -OC(O)NR<sup>11</sup>R<sup>11'</sup>.

14. The compound of Claim 13 wherein X is hydroxy and R<sup>1</sup>, R<sup>3</sup> and R<sup>3a</sup> are hydrogen and R<sup>9</sup> is -OCON(CH<sub>3</sub>)<sub>2</sub>.

15. The compound of Claim 1 wherein  $R^{2a}$  is a group of formula (a) or (b):



wherein  $Ar^2$ , B, C and Z are as defined above.

10 16. The compound of Claim 15 wherein B is either:

15 (a) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms an unsaturated heterocyclic group containing 3 or 4 carbon atoms and 0 or 1 additional nitrogen atoms and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the  $R^2$  group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino; or

20 (b) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms a saturated or unsaturated heterocyclic group containing 3 or 4 carbon atoms and 0 or 1 additional nitrogen atoms wherein said saturated or unsaturated heterocyclic group is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is optionally substituted, in addition to the  $R^2$  group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino; and

30 C is either:

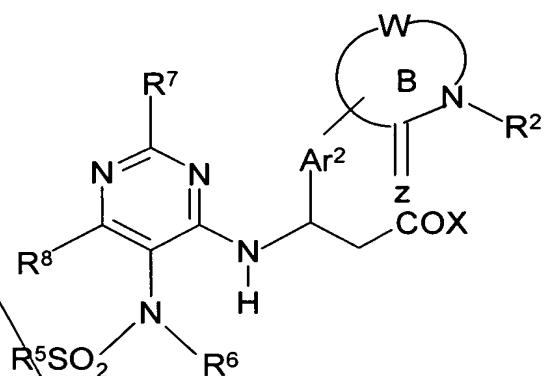
(a) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further the wherein the unsaturated heterocyclic group is optionally substituted, in addition to the  $R^2$  group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino; or

(b) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms a saturated or unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms wherein said saturated or unsaturated heterocyclic group is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, ~~oxazole~~, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is optionally substituted, in addition to the  $R^2$  group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino.

17. The compound of Claim 16 wherein  $R^1$ ,  $R^3$  and  $R^{3a}$  are hydrogen, and X is preferably hydroxy.

18. The compound of Claim 1 wherein the compounds has the formula IIIa, IIIb, IIIc, IIId, or IIIe:

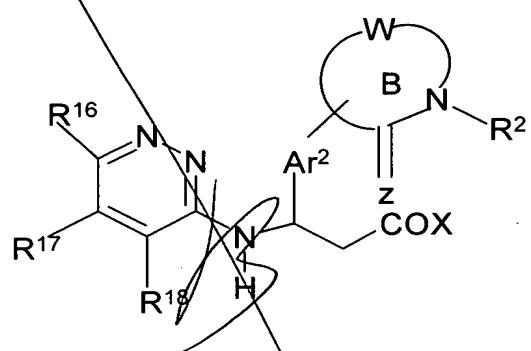
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IIIa

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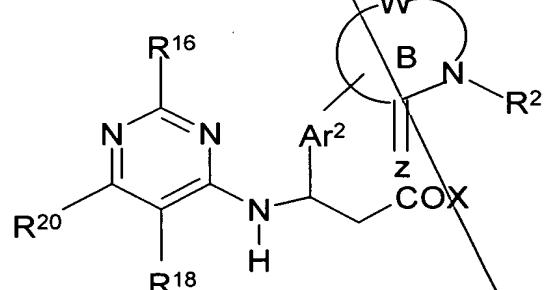
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IIIb

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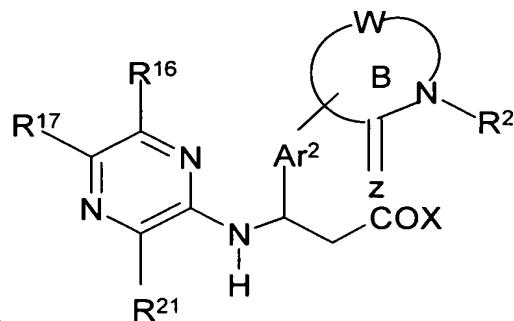
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IIIc

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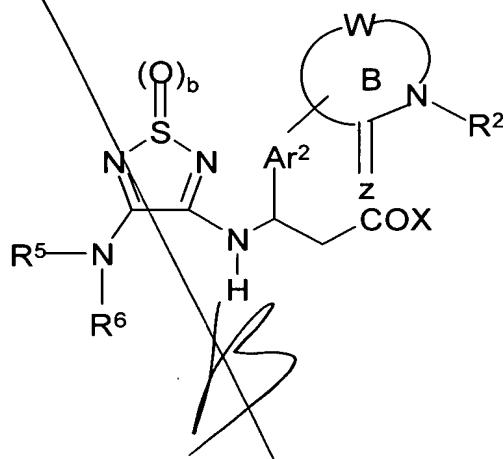
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III d

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III e

wherein:

X is hydroxyl or alkoxy;

Ar<sup>2</sup> is an aryl or heteroaryl group optionally substituted, in addition to ring B or C, with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio,

alkylsulfoxyl, substituted alkylsulfoxyl, alkylsulfonyl, and substituted alkylsulfonyl;

5        R<sup>5</sup> is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

10      R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -SO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

15      R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

20      R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

25      R<sup>18</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

30      R<sup>20</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

~~R<sup>21</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic; b is 1 or 2; and~~

5        B is a group wherein W, together with -C(=Z)NR<sup>2</sup>-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and -SO<sub>n</sub>- (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures

10      selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of with one or two substituent(s) selected from the group consisting

15      of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylenedioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxyl, substituted alkylsulfoxyl, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

20      R<sup>2</sup> is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl; and

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof

19. The compound of Claim 18 wherein B is either:

5 (a) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the  $R^2$  group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted 10 alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino; or

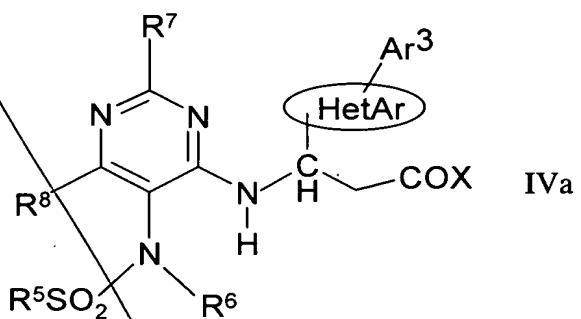
(b) a group wherein W, together with  $-C(=Z)NR^2$  where Z is -O-, forms a saturated or unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms wherein said saturated or unsaturated 15 heterocyclic group is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is optionally substituted, in addition to the  $R^2$  group, on any ring atom capable 20 of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino.

25 20. The compound of Claim 19 wherein  $Ar^2$  is preferably phenyl.

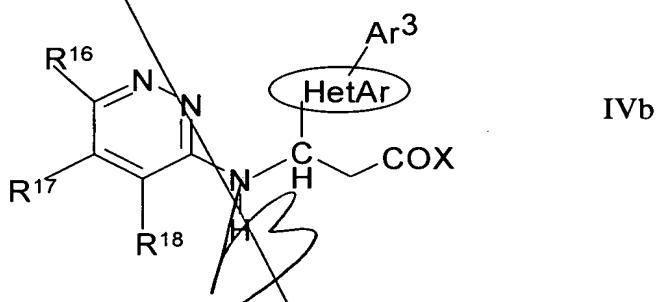
21. The compound of Claim 1 wherein  $R^{2a}$  is HetAr where HetAr is a nitrogen containing 6- membered heteroaryl that is optionally substituted with an aryl or substituted aryl group.

22. The compound of Claim 1 wherein the compounds are of formula IVa, IVb, IVc, IVd, or IVe:

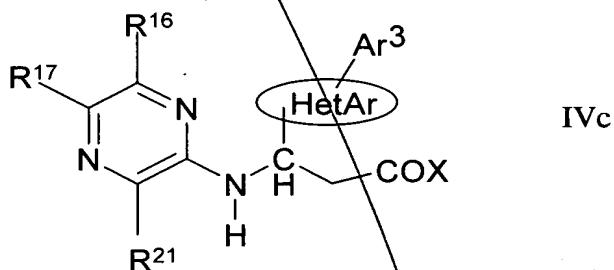
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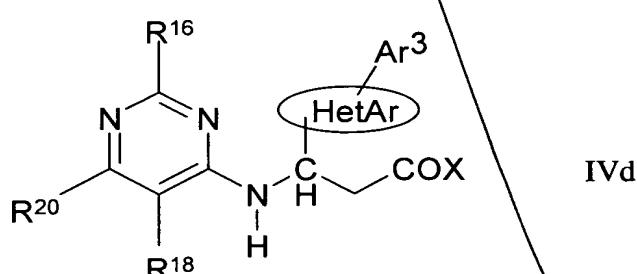
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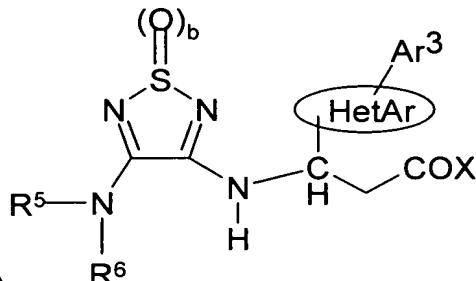
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IVe

wherein:

HetAr is a nitrogen containing heteroaryl group;

10 Ar<sup>3</sup> is aryl or substituted aryl;

$R^5$  is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

15 R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -SO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

**25** R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

$R^{16}$  and  $R^{17}$  are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

~~R<sup>18</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;~~

5 ~~R<sup>20</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;~~

10 ~~R<sup>21</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;~~

15 ~~b is 1 or 2; and  
X is hydroxyl; and  
and enantiomers, diastereomers and pharmaceutically acceptable salts thereof.~~

23. The compound of Claim 22 wherein HetAr is pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl and Ar<sup>3</sup> is substituted phenyl.

20 24. A method for treating a disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1-23.

25 25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1-23.

26. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claim 1 under conditions wherein said compound binds to VLA-4.

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*add  
β1  
add  
c4*